REMARKS

Claim Amendments

Claims 1, 9-10, and 26-29 are currently pending. Claim 29 has been canceled without prejudice. Claims 1 and 27 have been amended with this response.

Claim 1 has been amended in step (b) to recite that the test agent modulates the expression of UP and to include a second assay system capable of detecting an inhibition in the beta catenin pathway comprising cultured cells expressing UP; contacting the assay system of step (d) with the test agent of step (b); measuring the activity of the beta catenin pathway in the presence or absence of the test agent; and detecting an inhibition in the beta catenin pathway in the presence or absence of the test agent as a means to confirm that the test agent of step(b) is a beta-catenin inhibitory agent. Support for the amendment can be found throughout the specification and in original claim 16.

Claim 27 has been amended to clarify that the first assay system comprises cultured cells that express UP.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application.

35 USC §112, Second Paragraph, Rejections

Claim 29 was rejected under 35 USC 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 29 has been canceled rendering the rejection moot.

Applicants note that claim 29 was rejected as indefinite because the recitation of a "second assay system" is allegedly unclear in the absence of recitation of a "first assay system". Applicants have amended claim 1 to include the steps (d) – (f) in canceled claim 29. Claim 1 has been further amended to clarify that steps (a) – (c) pertain to a first assay system and steps (d) – (f) relate to a second assay system.

The Office further asserts that there is no distinguishable difference between the first and second assay systems. Applicants respectfully disagree. Steps (a)- (c) in the first assay system are designed to measure the expression of UP (specifically to detect a reduced expression of UP nucleic acid). Steps (d) – (f) in the second assay system is designed to measure the activity of the beta-catenin pathway (specifically to detect an inhibition in the beta catenin pathway). The first and second assay systems are designed to measure different parameters and are accordingly distinguishable assay systems.

35 USC §103 Rejections

Claims 1, 9, 26-27, and 29 were rejected under 35 U.S.C. 103(a) as being unpatentable over Pizzorno et al (WO 01/60985) ("Pizzorno"). Claim 29 has been canceled, rendering the rejection moot as to that claim. Applicants respectfully traverse the rejections of claims 1, 9, and 26-27.

According to the Office, Pizzorno teaches that uridine phosphorylase (UPase) activity and expression levels are upregulated in human tumors

compared to normal tissue and teaches that one can detect and evaluate the presence of malignant tumor cells by detecting UPase activity in a biological sample. The Office asserted that Pizzorno also teaches that a uridine phosphorylase inhibitor, such as antisense nucleic acids, can be used to inhibit the expression, function, or both of wild type UPase and/or mutant UPase (to treat cancer). The Office admitted that Pizzorno does not expressly teach a method of identifying antisense nucleic acids or RNAi-inducing dsRNA to inhibit the beta-catenin pathway, but argued that the method of Pizzorno would necessarily identify a beta-catenin pathway inhibitory agent since the method steps of Pizzorno necessarily and inherently comprise all the method steps recited in the rejected claims. The Office thereby concluded that the claims taken as a whole would have been *prima facie* obvious at the time of filing.

Under 35 U.S.C. § 103(a), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a predictable result or reasonable expectation of success. Also, the reference, or references in combination, must teach or suggest all the claim limitations. *See* MPEP §2143. Specifically, the Board of Patent Appeals and Interferences (BPAI) has stated that:

> [A]n examiner must make "a searching comparison of the claimed invention — including all its limitations - with the teaching of the prior art." In re Ochiai, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d, 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka,* 490 F.2d 981, 985 (CCPA 1974)).

See also, Ex parte Shepard, BPAI, Appeal 2008-0401, page 7 (Jan. 3, 2008)(unpublished) (BPAI reversed the Examiner's rejection of obviousness, because "having failed to demonstrate that the references teach the limitations of claim 11, the Examiner failed to establish a prima facie case of obviousness for claims 17 or 18 which depend from claim 11.").

Thus, to establish a prima facie case of obviousness, Pizzorno must teach a method comprising each and every step of the claimed assay. That is, Pizzorno must teach a screening assay comprising each of the following steps:

(a) providing a first assay system comprising a uridine phosphorylase (UP) nucleic acid;

(b) contacting the assay system with a test agent that modulates the expression of UP; and

(c) detecting reduced expression of UP nucleic acid in the presence of the test agent compared to the expression in the absence of said test agent, wherein reduced expression of said UP nucleic acid in the presence of the test agent compared to the expression in the absence of said test agent identifies the test agent as a candidate beta catenin pathway inhibitory agent;

(d) providing a second assay system capable of detecting an inhibition in the beta catenin pathway comprising cultured cells expressing UP,

(e) contacting the assay system of step (d) with the test agent of step (b);

(f) measuring the beta catenin pathway in the presence or absence of the test agent; and

(g) confirming that the test agent of step (b) is a beta-catenin inhibitory agent by detecting an inhibition in the beta catenin pathway in the presence or absence of the test agent.

Applicants submit that Pizzorno fails to teach or suggest all of the elements of the claimed subject matter. Pizzorno is directed to diagnostic and therapeutic methods relating to UPase (i.e., UP) and not to screening assay methods. Pizzorno specifically teaches that certain tumors contain mutated UPase that is resistant to the inhibitory effect of UPase inhibitors. Accordingly, they suggest identifying mutations in UPase associated with UPase inhibitor resistance to diagnose and treat cancer. Pizzorno makes no mention whatsoever of the beta-catenin pathway or an association between UP and the beta-catenin pathway. Accordingly, Pizzirno fails to contemplate, much less

teach or suggest, a screening assay method employing a second assay system to detect a change (inhibition) in the beta catenin pathway.

Furthermore, one skilled in the art would not have been motivated to modify the teachings of Pizzorno to arrive at the presently claimed screening assay methods. As discussed, Pizzorno is directed to diagnostic and therapeutic methods, not to screening assay methods, and fails to even recognize or contemplate a connection between UP and the beta-catenin pathway. Thus, Pizzorno is silent as to assays that could be used to measure the activity of the beta-catenin pathway. In the absence of any teaching or suggestion whatsoever of a connection between UP and the beta catenin pathway, one skilled in the art would not have been motivated by the teachings of Pizzorno to pursue a method that utilizes an agent that modulates UP in an assay system that detects changes in the beta catenin pathway.

Applicants submit that the Office has failed to establish a *prima facie* case of obviousness for the reasons set forth above. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection based on the teachings of Pizzorno.

Claims 1, 9-10, and 26-29 were rejected under 35 U.S.C. 103(a) as being unpatentable over Verma et al. *(Clinical Cancer Research,* 2003, 9:1291-1300) in view of Miyashita et al. *(Cancer,* 2002, 94:2959-2966), Deneen et al. *(Molecular and Cellular Biology,* 2003, 23:3897-3908), Pizzorno et al. (WO 01/60985 A2), Deneen et al. *(Cancer Research,* 2003, 63:4268-4274), and Monga et al. *(Gastroenterology,* 2003, 124:202-216).

The Office asserted that Verma et al. teach that one can use cells that overexpress beta-catenin to identify an inhibitor of the beta-catenin signaling pathway, such as siRNA targeted to beta-catenin. Verma te al. also allegedly shows that siRNA targeted to beta-catenin reduces beta-catenin expression, as well as tumor cell proliferation. In addition, the Office maintained that Verma et al. shows that siRNA targeted to beta-catenin reduces the expression levels of beta-catenin dependent genes, such as c-myc and cyclin DI. The Office admitted that

Verma et al. do not teach using an siRNA/PM0 targeted to uridine phosphorylase to identify a beta-catenin pathway inhibitory agent.

According to the Office, Miyashita et al. teaches that uridine phosphorylase is highly expressed in the majority squamous cell carcinoma cells and that its expression level is correlated with poor prognosis. Miyashita et al. also allegedly teach that amplification of the protooncogene cyclin D1 is associated with poor prognosis of oral squamous cell carcinoma.

The Office asserted that Deneen et al. *(Molecular and Cellular Biology)* teach that cyclin D1 and uridine phosphorylase are upregulated by EWS/ETS fusion proteins in NIH3T3 cells and suggest that cyclin D1 and uridine phosphorylase are EWS/ETS target genes playing a role in EWS/ETS-mediated oncogenesis/tumorigenesis.

With respect to Deneen et al. *(Cancer Research)*, the Office stated that Deneen et al. teach that uridine phosphorylase is upregulated and overexpressed in a number of human tumor cells and demonstrate that uridine phosphorylase is a biologically relevant EWS/ETS target gene. The Office further stated that Deneen suggests that uridine phosphorylase contributes to pathways that initiate cellular proliferation and promote cellular transformation.

The Office reiterated that Pizzorno et al. teach that uridine phosphorylase (UPase) activity and expression levels are upregulated in human tumors compared to normal tissue and that one can detect the presence of a malignant tumor cell by detecting UPase activity. The Office stated that Pizzorno also teaches that a uridine phosphorylase inhibitor, such as an antisense against UP, can be used to treat cancer.

Finally, the Office alleged that Monga et al. teach that one can use a PM0 antisense molecule to identify a beta-catenin signaling pathway inhibitor, which also functions as a cell proliferation inhibitor, wherein the identification process involves a comparison between PM0 antisense-treated cells and negative control antisense-treated cells.

Based on these teachings, the Office argued that it would have been obvious to one of ordinary skill in the art at the time the invention was made to

make an siRNA or a PM0 antisense targeted to a UP nucleic acid and to treat tumor cells with the siRNA/PM0 to identify whether the siRNA/PM0 inhibits uridine phosphorylase expression in the tumor cells, wherein such identification also identifies an inhibitor of the beta-catenin signaling pathway involving cyclin Dl.

The Office reasoned that one of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success, because Pizzorno teaches that an inhibitor (such as an antisense molecule) of uridine phosphorylase is a useful anti-cancer agent and thus identifying a nucleic acid-based uridine phosphorylase inhibitor was an art-recognized goal at the time the invention was made. The Office stated that there would have been a reasonable expectation that an inhibitor of uridine phosphorylase would inhibit the beta-catenin signaling pathway because (1) cyclin D1 and UP are often co-upregulated and overexpressed in tumor cells and (2) cyclin D1 was suggested to be a beta-catenin-dependent gene.

According to the Office, based on the overlapping expression/activity levels and the overlapping functional roles (ie as a growth regulator) between uridine phosphorylase, cyclin D1, and beta-catenin in tumor cells/proliferating cells, one of ordinary skill in the art would have reasonably predicted that an inhibitor of uridine phosphorylase is likely to also inhibit beta-catenin signaling. Further, it would have been obvious to one of ordinary skill in the art to use tumor cells that not only overexpress UPase and but also have activated beta-catenin signaling pathway to identify a PM0 or an siRNA molecule that inhibits not only tumor cell growth but also the expression levels of UPase. Thus, the Office concluded that the claims taken as a whole would have been *prima facie* obvious at the time of filing.

Applicants respectfully disagree. Under 35 U.S.C. § 103(a), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a

predictable result or reasonable expectation of success. Also, the reference, or references in combination, must teach or suggest all the claim limitations. *See* MPEP §2143.

Initially, to establish a *prima facie* case of obviousness, there must be some suggestion or motivation to modify the reference or to combine reference teachings and there must be a predictable result or reasonable expectation of success. The Supreme Court in *KSR v. Teleflex* has instructed that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex, Inc.*, 550 US 398, 127 S. Ct. 1727, 1740 (2007). Rather, the Court emphasized the importance of identifying a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does. *KSR* at 1741.

Applicants submit that the Office has not provided a reason as to why one skilled in the art would seek to combine the teachings of the chosen references to arrive at the presently claimed invention. Specifically, the Office has not provided a reason as to why one skilled in the art concerned with UP would seek references relating to EWS/ETS fusion proteins or references relating to beta catenin. Miyashita teaches that UP, EGFR, cyclin D1 and p53 are up-regulated in squamous cell carcinoma cells. Miyashita makes no mention of beta catenin and therefore makes no connection between UP and beta catenin; nor does it make a connection between UP and cyclin D1 except to note that both can be a biomarker for squamous cell carcinoma (SCC). Miyashita is concerned with the use of UP as a biomarker for SCC and makes no suggestion to screen for UP inhibitors. As discussed above, Pizzorno is directed to diagnostic and therapeutic methods relating to and not to screening assay methods. Pizzorno teaches that certain tumors contain mutated UP that is resistant to the inhibitory effect of UP inhibitors and suggests identifying mutations in UP associated with UP inhibitor resistance to diagnose and treat cancer. Pizzorno makes no mention whatsoever of the beta-catenin pathway or an association between UP and the beta-catenin pathway. Deneen et al. *(Molecular and Cellular Biology)*

teach that cyclin D1 and UP are two of ***over one hundred*** genes modulated by EWS/ETS fusion proteins in NIH3T3 cells and suggest that cyclin D1 and UP may be EWS/ETS target genes that play a role in EWS/ETS-mediated oncogenesis/tumorigenesis. Deneen et al. suggests that the up-regulation of UP alters glucose metabolism (Applicants note that cyclin D1 is involved in cell cycle regulation, not glucose metabolism). Dineen is concerned only with EWS/ETS and therefore makes no mention of the beta catenin pathway; nor does it provide a suggestion to screen for UP inhibitors. Deneen et al. *(Cancer Research)* teach that UP is upregulated and overexpressed in a number of human tumor cells and demonstrate that uridine phosphorylase may be a direct target of EWS/ETS. Deneen et al. suggest that UP may contribute to pathways that initiate cellular proliferation but not tumor induction or maintenance. Dineen et al. makes no mention of the beta catenin pathway; nor does it provide a suggestion to screen for UP inhibitors.

Accordingly, none of these references that discuss UP are directed to screening assays for UP inhibitors and none of the references mention the beta catenin pathway or a connection between UP and the beta catenin pathway. And while Miyashita and Pizzorno may implicitly suggest to seek inhibitors of UP to inhibit cell proliferation in cancer cells, none of the references alone or in combination suggest to pursue a screening assay that additionally involves measuring the activity of the beta-catenin pathway and therefore would not motivate one to seek the teachings of Verma and Monga.

Likewise, one of ordinary skill in the art would not seek the teachings of Miyashito, Pizzorno, and the two Dennen references based on the teachings of Verma and Monga. Verma teaches that siRNA against beta catenin reduces the level of beta catenin and beta catenin-dependent gene expression, i.e., c-myc and cyclin D1, and inhibits cell proliferation (but does not increase apoptosis) in colon cancer cells. Verma fails to mention UP or screening assays. Monga teaches that antisense against beta catenin results in decreased cell proliferation and increased apoptosis in liver cells. Monga et al. also teaches that cyclin D1 and c-myc are **not** targets of beta catenin in developing liver cells. Like Verma,

Monga et al. does not mention UP or screening assays, or suggest to seek indirect (i.e., upstream) inhibitors of beta catenin. Therefore, there is no motivation in either Verma or Monga to seek an inhibitor of any protein other than beta-catenin.

The fact that UP, EWS/ETS, and beta catenin are involved cancer cell growth does not provide a proper nexus (i.e., specific suggestion) for combination because there are hundreds of genes involved in cancer cell growth (i.e, it is not a unique characteristic). Without the benefit of the teaching provided in Applicant's specification (i.e., the connection between UP and the beta catenin pathway), one skilled in the art would not have been motivated to seek the teachings of the particular combination of references cited by the Office.

Furthermore, even if one would have been motivated to combine the teachings of the cited references, such combination still would not have met the requirements for a finding of obviousness because one skilled in the art would not have had a reasonable expectation that a UP inhibitor would be useful in a screening assay to inhibit the activity of the beta catenin pathway based on the teachings in the specified references. There is no teaching in the cited art that provides a connection between UP and the beta catenin pathway such that one skilled in the art would reasonably expect that a UP inhibitor would also inhibit the beta catenin pathway. Thus, not only do the combination of references fail to suggest to one skilled in the art to make and use a screening assay that involves using a UP inhibitor in an assay system that measures beta catenin pathway activity, but they also fail to provide any reasonable expectation that such UP inhibitor would function to inhibit the beta catenin pathway if such an assay was pursued.

The Office stated that there would have been a reasonable expectation that an inhibitor of uridine phosphorylase would inhibit the beta-catenin signaling pathway because (1) cyclin D1 and UP are often co-upregulated and overexpressed in tumor cells and (2) cyclin D1 was suggested to be a beta-catenin-dependent gene. However, applicants submit that such findings fail to establish a sufficient nexus such that one skilled in the art would reasonably

expect that a UP inhibitor would also inhibit the beta catenin pathway. The fact that cyclin D1 and UP are often up-regulated in tumor cells does not suggest any type of modulating or regulatory relationship between the two proteins. First, numerous genes are up-regulated in cancer cells without any apparent regulatory relationship to one another. Moreover, cyclin D1 is involved in the cell cycle pathway, while UP is involved in glucose metabolism. In the absence of further teaching establishing a connection between UP and cyclin D1, Applicants submit that a teaching of co-up-regulation does not suggest a relationship between the two proteins. Furthermore, the fact that an inhibitor of beta-catenin may inhibit the expression of cyclin D1 in certain cells (as taught by Verma), but not others (as taught by Monga) provides no teaching or suggestion whatsoever that an inhibitor of UP may inhibit the beta catenin pathway (based only on an observation that cyclin D1 and UP are both activated in certain cells).

Applicants submit that one skilled in the art would not have had a reasonable expectation that a UP inhibitor would be useful in a screening assay to inhibit the activity of the beta catenin pathway based on the combined teachings in the specified references for the reasons provided.

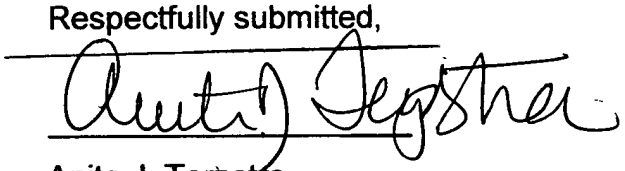
Finally, in the absence of such expectation, Applicants submit that the combination of references fails to teach or suggest all the steps recited in the claimed assay methods. Specifically, the references fail to teach a screening assay which requires at least (1) contacting a first assay system comprising UP nucleic acid with a test agent that modulates the expression of UP; (2) detecting reduced expression of UP nucleic acid in the presence of the test agent; (3) contacting a second assay system capable of detecting an inhibition in the beta catenin pathway with the same test agent and (4) measuring the activity of the beta catenin pathway.

Applicants submit that the Office has failed to establish a *prima facie* case of obviousness for the reasons set forth above. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection based on the teachings of Verma et al., Miyashita et al., Deneen et al. *(Molecular and Cellular Biology),* Pizzorno et al., Deneen et al. *(Cancer Research),* and Monga et al.

Conclusion

In view of the above remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue. If the Examiner has any questions regarding this response, she is invited to call the undersigned attorney.

Respectfully submitted,



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Anita J. Terpstra
Registration No. 47,132

McDONNELL BOEHNEN HULBERT & BERGHOFF, LLP
300 South Wacker Drive
Chicago, Illinois 60606
TEL (312) 913-0001
FAX (312) 913-0002